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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,882	05/17/2006	Dominique Jean-Pierre Mabire	PRD-2124USPCT	8486

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EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,882	MABIRE ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8 and 10-29* is/are pending in the application.

4a) Of the above claim(s) *8,10-13 and 17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 14-16, and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's submission filed July 10, 2009 has been received and entered into the present application.

Status of claim

Claims 5, 7, 9, and 30 have been canceled and claims 8, 10-13, and 17-28 have been withdrawn. Claims 1-4, 6, 14-16, and 29 are under examination in the instant office action.

Claim Objection

Claim 1 is objected because of the following informalities: typographical errors. The phrase "they may taken together form a bivalent radical" in line 4 at page 4 should be corrected to --"they may be taken together to form a bivalent radical" --. The term "or" should be added before the formula (c-11) in line 11 at page 3.

Claims 2-3 are objected to under 37 CFR 1.75(c), as being of improper dependent form or failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 2-3 recites that "R^4, R^5, R^6 are each indecently selected

from hydrogen, halo, or C1-6alkyl" and "R^4, R^5, R^6 are each indecently selected from hydrogen or halo", respectively. However, when X is N; n is 0, 1, or 2; R^1 is C_{1-6} alkyl; R^2 is hydrogen, and R^3 is a group of formula (b-1), t is 0 and Z is formula (c-2), at least one of R^4, R^5 and R^6 is other than hydrogen, halo, trihalomethyl, C_{1-6} alkyl, or C_{1-6} alkyloxy, thus claims 2-3 do not further limit the claim 1 when R^3 is a group of formula (b-1), t is 0 and Z is formula (c-2).

Claim 29 is objected as being dependent from the non-elected group.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3 and 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All dependent claims are included in this rejection.

Claims 2-3 recites that "R^4, R^5, R^6 are each indecently selected from hydrogen, halo, or C1-6alkyl" and "R^4, R^5, R^6 are each indecently selected from hydrogen or halo", respectively. However, the instant claim 1 recites the following limitation "with the proviso that when X is N; n is 0, 1, or 2; R^1 is C_{1-6} alkyl; R^2 is hydrogen, R^3 is a group of formula (b-1), t is 0 and Z is formula (c-2); and at least one of R^4, R^5 and R^6 is other than hydrogen, halo, trihalomethyl, C_{1-6} alkyl, or C_{1-6} alkyloxy. Thus, it is unclear whether or not the proviso recited in claim 1 applies to claims 2-3 because when R^3 is a group of formula (b-1), t is 0 and Z is formula (c-2), at least one of R^4, R^5 and R^6 can not be other than hydrogen, halo, trihalomethyl, C_{1-6} alkyl, or C_{1-6} alkyloxy.

For the examination purpose, the claims are interpreted with the proviso, thus formula (c-2) can not be a choice for Z.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein R^7 is hydrogen and R^4, R^5, R^6 are selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C1-6alkyl, C1-6alkyloxy, di(C1-6alkyl)amino, di(C1-6alkyl)aminoC 1-6alkyloxy or C1-6alkyloxycarbonyl, does not reasonably provide enablement for remaining scope wherein R^7 is taken together with R^1 to form a bivalent radical of formula -CH=CH-CH=CH- and R^5 and R^6 are taken together form a bivalent radical of formula formula (d-1), (d-2), (d-3), or (d-4). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There is no reasonable basis for assuming that the myriad of compounds embraced by all the generic claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey* 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical

art. Also note the criteria for enablement as set out in *In re Wands* cited in MPEP 2164.01(a), August 2000 edition, which includes factors such as:

1) Breadth of the claims- The claim is drawn to compounds defined by formula I, which are allegedly effective for inhibiting nuclear enzyme poly(ADP-ribose) polymerase (PARP). The formula I is drawn to substituents layered on top of substituents that vary independently and lead to compounds of a wide variety of structures. These compounds encompass molecules that widely vary in the physical and chemical properties such as size, molecular weight, acidity, basicity, and properties that are known in the art to greatly influence pharmacokinetic and pharmacodynamic parameters, not to mention the ability to productively bind to claimed biological target molecules. The claims cover compounds easily in the millions given the number of possible rings, ring systems covered by the claims' scope along with varying choices for remaining variables. Especially, when R^7 is taken together with R^1 to form a bivalent radical of formula -CH=CH-CH=CH- and R^5 and R^6 are taken together to form a bivalent radical of formula formula (d-1), (d-2), (d-3), or (d-4), the resulted compounds will have different core structures, which belongs to different chemical classes;

2) Level of unpredictability in the art- The invention is pharmaceutical in nature as it involves interaction with to a particular type of poly(ADP-ribose) polymerase enzyme. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See *In re Fisher* 166 USPQ 18.

3) Direction or guidance- As stated above, the compounds made are not representative of the instant scope but are closer to each other than to remaining scope. In particular, when R^7 is

taken together with R^1 to form a bivalent radical of formula -CH=CH-CH=CH- and R^5 and R^6 are taken together to form a bivalent radical of formula formula (d-1), (d-2), (d-3), or (d-4), the resulted bulky heterocylic rings will have different core structures from quinolinone or quinoxalinone ring, which may be chemically incompatible with the method of use embraced in the instant claims. Specification offers no teachings or suggestion as to how to make and use these compounds. Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.";

4) State of the prior art- The pharmaceutical art is unpredictable and target compounds need to be individually assessed for viability. The compounds are substituted quinolinone or quinoxalinone derivatives with a heterocyclic ring bearing additional ring substitutions. No such compounds are known from a search in the prior art for even one use much less for activity relied on herein;

5) Working examples- The specification gives some *in vitro* test results on PARP inhibitory effects of limited number of preferable compounds, however it is too homogeneous to provide a clear evaluation of which rings attached to quinolinone or quinoxalinone with various substitutions out of the many claimed might affect potency to a large or small degree. The pharmaceutical art is unpredictable and target compounds need to be individually assessed for viability. Extremely broad generalizations as found in the instant claims are in contradiction with the basis of quantitative structure-activity-relationship (QSAR).

6) The quantity of experimentation needed: In view of the above considerations, one of ordinary skill in the art would be presented with an unpredictable amount of research effort to identify a compound out of the plethora of possibilities encompassed by the formula I that would have useful biological properties.

Genentech Inc. v. Novo Nordisk A/S (CA FC)42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

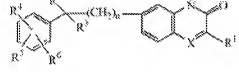
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 6, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,028,606.

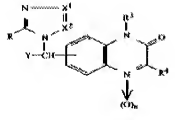
The instant invention is drawn to a compound of the following formula (I) and a pharmaceutical composition comprising the compound of formula (I) and the following compound is recited in the instant claim 4. The elected species is free of prior art, thus examination is further extended the next species wherein X is N; n is 0, 1, or 2; R^1 is C_{1-6} alkyl; R^2 is hydrogen, R^3 is a group of formula (b-1), t is 0 and Z is formula (c-2); and at least one of R^4, R^5 and R^6 is other than hydrogen, halo, trihalomethyl, C_{1-6} alkyl, or C_{1-6} alkyloxy.

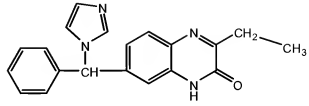


(I)

US patent 5,028,606 teaches substituted quinoxalinone derivatives (abstract and Table 9), wherein Y is Ar1 , Ar2, hydrogen; C_{1-10} alkyl; C_{3-7} cycloalkyl; C_{1-6} alkyl; C_{2-6} alkenyl or C_{2-6}

alkynyl; and n is 0 or 1 and discloses the following compound (claim 1 and Table 9, compound 115):





It further teaches that the Ar2 is phenyl substituted with 1, 2 to 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkyloxy, cyano, amino, mono- and di(C_{1-6} alkyl)amino, nitro, carboxyl, formyl and C_{1-6} alkyloxycarbonyl (column 2, line 42-49 and claim 1).

The reference also teaches a pharmaceutical composition of substituted quinoxalinone derivatives with a pharmaceutically acceptable carrier (column 20, lines 47-58).

With regard to the instant claims 29, which are directed to a product made by the process of the instant claim 13, the reference discloses the same processes of making the substituted quinoxalinone derivatives as recited in the instant claim 13 (column 8, line 61-column 9, line 23 and column 10, lines 37-65). In the alternative, when the reference teaches a product that appears to be the same as, or an obvious variant of, the product set forth in a product-by-process claim although produced by a different process, either 102 or 103 rejection can be properly made. See *In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983) and *In re Thorpe*, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985). See also MPEP §2113. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the

product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

The reference does not explicitly disclose a specific embodiment wherein the phenyl ring is substituted with a substituent other than hydrogen, halo, trihalomethyl, C_{1-6} alkyl, or C_{1-6} alkyloxy although the next species is a species of the genus disclosed in US patent 5,028,606, wheerein Y is phenyl substituted with hydroxy, cyano, amino, mono- and di(C_{1-6} alkyl)amino, nitro, carboxyl, formyl and C_{1-6} alkyloxycarbonyl; n is 0; and R4 is C_{1-6} alkyl.

It would have been prima facie obvious to one having ordinary skill in the art at the time of the invention was made to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989). In addition, the reference already discloses the phenyl ring can be substituted with other than hydrogen, halo, trihalomethyl, C_{1-6} alkyl, or C_{1-6} alkyloxy such as hydroxy, cyano, amino, mono- and di(C_{1-6} alkyl)amino, nitro, carboxyl, formyl and C_{1-6} alkyloxycarbonyl. Thus, it would have been prima facie obvious to one having ordinary skill in

the art at the time of the invention was made to modify the compound of US patent 5,028,606 to arrive at the claimed compound by having the phenyl ring substituted with hydroxy, cyano, amino, mono- and di(C_{1-6} alkyl)amino, nitro, carboxyl, formyl or C_{1-6} alkyloxycarbonyl because such modifications have already been suggested by US patent 5,028,606.

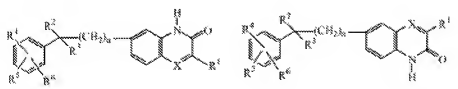
Provisional Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

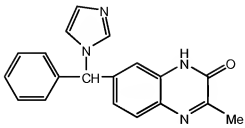
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

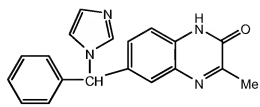
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6, 14-16, and 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 7 of copending Application No. 10/595891 in view of US 5,028,606. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are directed to substituted quinolinone and quinoxaline compounds of the almost identical structure and the same substitutions. The difference between the instant compounds and the compounds of the '891 application is the position of the substitution (position 7 for the instant application and position 6 for the '891 application) as shown below:



As stated in the first 102 rejection above, US 5,028,606 teaches the same compounds as the instant invention. It further shows that position isomers, which have a substitution in the either position 6 or position 7 of quinoxaline ring, are possible while retaining the same biological activity. The following is an example of positional isomers shown in US 5,028,606.





It would have been obvious to a person of ordinary skill in the art at the time the invention was made to change substitution position to get another positional isomer with a reasonable expectation of success. MPEP 2144.09 states "Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). In addition, US 5,028,606 already suggests making positional isomers of the same core structure as the instant invention in the same positions while retaining the same biological activity. One skilled in the art would have been motivated to prepare positional isomers as taught by the prior art with the expectation of obtaining another homologous compound which will retain the same activity.

This is a provisional obviousness-type double patenting rejection.

Since a terminal disclaimer has not been filed, the above double patenting rejection is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 8:00-5:00 Monday-Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614
Bbs

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Examiner, Art Unit 1614